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$B(C_6F_5)_3$-Catalyzed Diastereoselective and Divergent Reactions of Vinyldiazo Esters with Nitrones: Synthesis of Highly Functionalized Diazo Compounds

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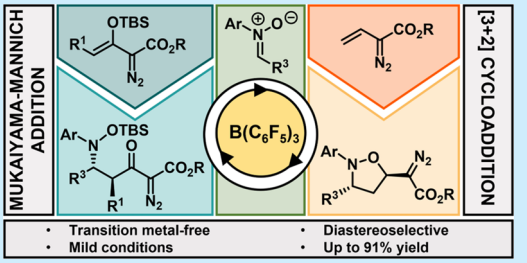
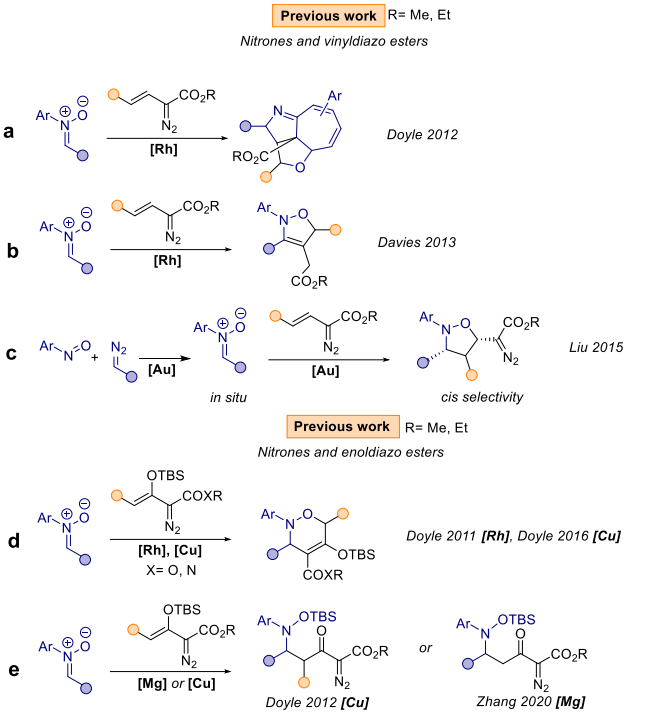
ABSTRACT: Herein we report a mild, transition-metal-free, highly diastereoselective Lewis acid catalyzed methodology toward the synthesis of isoxazolidine-based diazo compounds from the reaction between vinyldiazo esters and nitrones. Interestingly, the isoxazolidine products were identified to have contrasting diastereoselectivity to previously reported metal-catalyzed reactions. Furthermore, the same catalyst can be used with enol diazo esters, prompting the formation of Mukaiyama−Mannich products. These diazo products can then be further functionalized to afford benzo[*b*]azepine and pyrrolidinone derivatives.



Over the past decade, alkenyldiazo compounds have been shown to be versatile reagents for the preparation of a wide variety of hetero- and carbocycles. The reactivity of alkenyldiazo compounds has been found to be influenced by the substitutions on the vinyl moiety or the choice of a catalyst used for the desired transformation.[1] Vinyldiazo compounds have been mainly used in the presence of transition metals (i.e., Rh, Ag, Au, Cu) to form electrophilic metal carbene intermediates, which then undergo [3+*n*] (*n* = 2−4) cycloaddition reactions with dienophiles, including nitrones (Scheme 1).[2] Though not as prevalent, and again mostly in the presence of transition metals, there have been several reports on utilizing alkenyldiazo reagents for their nucleophilic character, originating from the vinyl functionality, to form acyclic and cyclic compounds, where the diazo functionality remains intact.[3] The remaining diazo group can then be used in further synthetic transformations (Scheme 1c,e).

In the past few years, we and others have shown that the boron Lewis acid, $B(C_6F_5)_3$, activates α-aryl α-diazo esters in a similar fashion to metal catalysts, and this has been utilized for transition-metal-free cyclization, alkenylation, or X−H insertion reactions. Moreover, these transformations are highly diastereoselective, which has been attributed to the steric hindrance around the boron center.[4] In our studies we have observed that the activation of the diazo moiety strongly depends on the nature of the diazo compound, so there are cases where the diazo functionality could remain intact and be activated at later stages. With this in mind, we were curious whether borane catalysts can be employed for cycloaddition reactions in the presence of vinyldiazo esters to access heterocyclic, highly functionalized diazo compounds (Scheme 2).

Scheme 1. Previous Work



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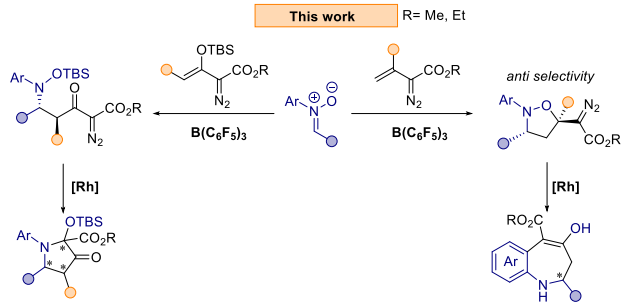
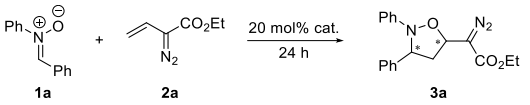
Scheme 2. Work Presented in This Manuscript



Accessing isoxazolidine-derived diazo reagents has caught our interest due to the heterocycle's labile N−O bond, which can undergo ring-opening reactions to access novel bioactive heterocycles, including pyrrolidines and benzoazepines.[5] Moreover, fused bicyclic isoxazolidines have been found in natural products and can possess cytotoxic, antifungal, or anti-inflammatory activities.[6] The most straightforward synthetic strategy to access isoxazolidine-derived scaffolds is via a thermal 1,3-dipolar cycloaddition of nitrones and alkenes, which often results in poor diastereoselective and regioselective control.[7] Furthermore, applying high temperatures is not compatible with the unstable alkenyldiazo reagents, which can readily undergo decomposition.[8] As such, accessing isoxazolidine-derived diazo esters under mild conditions and in high diastereoselectivities remains challenging and, to the best of our knowledge, such methodology has only been reported in the presence of a gold catalyst (Scheme 1a).[3b]

To this end we initiated our studies by exploring the optimal reaction conditions for the cycloaddition of nitrone **1a** with alkenyldiazo ester **2a** as our model substrates (Table 1). The initial control reactions, carried out in the absence of a catalyst at room temperature and at 80 °C in 1,2-dichloroethane (1,2-$C_2H_4Cl_2$), showed no product formation after 24 h, and diazo decomposition was observed (entries 1 and 2). However, when the same reaction was carried out at 40 °C for 36 h, the formation of isoxazolidine **3a** was observed in good diastereoselectivity (dr 9:91), though in poor yield (18%) (entry 3). Utilizing 20 mol % $BF_3{\cdot}OEt_2$ did not improve the yield or the diastereoselectivity (entry 4). However, when 20 mol % $B(C_6F_5)_3$ was used as a catalyst, not only was the yield of **3a** improved to 60% but also the diastereoselectivity was inversed (dr 83:17) (entry 5). Other aryl fluorinated boranes, such as $B(3,4,5\text{-}F_3C_6H_2)_3$ [$B(3,4,5\text{-}Ar^F)_3$] and $B(2,4,6\text{-}F_3C_6H_2)$[$B(2,4,6\text{-}Ar^F)_3$], failed to catalyze the cycloaddition reaction efficiently giving **3a** in just 28% and 23% yield and in poor diastereoselectivities (38:62 and 48:52) (entries 6 and 7). When BPh_3 was screened as a catalyst, less than 5% of product formation was observed (entry 8), and Brønsted acidic TfOH failed to catalyze the reaction completely (entry 9). Decreasing the catalytic loading of $B(C_6F_5)_3$ from 20 to 10 and 5 mol % resulted in both poorer diastereoselectivities and yields (entries 10, 11, and 14). Lastly, different solvents were screened for the cycloaddition reaction (entries 12−19). When the reaction was carried out in dichloromethane (CH_2Cl_2), the dr remained unchanged, and the yield improved slightly to 63% (entry 16). Both trifluorotoluene ($C_6H_5CF_3$) and hexane improved the diastereoselectivities to 87:13 and 89:11, though the overall yields were decreased to 56% and 45%, respectively (entries 17 and 18). Coordinating solvents such as acetonitrile (MeCN) and tetrahydrofuran (THF) either completely failed to form

Table 1. Reaction Optimization for the Cycloaddition Reaction



1a 2a 3a

Entry	Catalyst	Solvent	Temp (°C)	dr[a] (anti/syn)	Yield[b] of **3a** (%)
1		$C_2H_4Cl_2$	rt		
2		$C_2H_4Cl_2$	80		
3[c]		$C_2H_4Cl_2$	40	9:91	18
4	$BF_3{\cdot}OEt_2$	$C_2H_4Cl_2$	40	18:82	15
5	$B(C_6F_5)_3$	$C_2H_4Cl_2$	40	83:17	60
6	$B(3,4,5\text{-}Ar^F)_3$	$C_2H_4Cl_2$	40	38:62	28
7	$B(2,4,6\text{-}Ar^F)_3$	$C_2H_4Cl_2$	40	48:52	23
8	BPh_3	$C_2H_4Cl_2$	40		<5
9	TfOH	$C_2H_4Cl_2$	40		
10[d]	$B(C_6F_5)_3$	$C_2H_4Cl_2$	40	71:29	44
11[e]	$B(C_6F_5)_3$	$C_2H_4Cl_2$	40	57:43	26
12	$B(C_6F_5)_3$	Toluene	40	91:9	74
13	$B(C_6F_5)_3$	Toluene	RT	91:9	72
14[d]	$B(C_6F_5)_3$	Toluene	RT	80:20	42
15	$B(C_6F_5)_3$	THF	40	65:35	32
16	$B(C_6F_5)_3$	CH_2Cl_2	40	83:17	63
17	$B(C_6F_5)_3$	$C_6H_5CF_3$	40	87:13	56
18	$B(C_6F_5)_3$	Hexane	40	89:11	45
19	$B(C_6F_5)_3$	MeCN	40		

[a]Determined from ^{1}H NMR spectra of the crude reaction mixture. [b]Isolated yields of the diastereomeric mixture. [c]Reaction ran for 36 h. [d]10 mol % $B(C_6F_5)_3$. [e]5 mol % $B(C_6F_5)_3$.

the isoxazolidine product (entry 19) or **3a** was obtained in a lower yield of 32% and in poor diastereoselectivity (65:35) (entry 13). This is presumably due to the deactivation of the borane catalyst. The most favorable reaction conditions were obtained when the reaction was carried out in toluene at either room temperature or 40 °C (entries 12 and 13). Not only was the yield of **3a** improved to 72−74% but an excellent diastereoselectivity (91:9) was also observed. We decided to use the conditions in entry 12 as the optimized conditions for the scope investigation.

With the optimized conditions in hand, we explored a substrate scope for the reaction (Scheme 3). First, nitrones **1a**−**1i** and **1p** (see Figure S1) with different substitutions at the R^1 position were explored. In general, *para*-substituted halogen groups (*p*-F and *p*-Cl) on the phenyl ring resulted in excellent yields [82% (**3e**) and 84% (**3f**), respectively] and excellent diastereoselectivities (92:8 and 91:9, respectively). Notably, when the *p*-CF_3 group was present, the isoxazolidine **3d** was formed as a single diastereoisomer in a good yield of 76%. Furthermore, both 2-naphthyl and 1-naphthyl substitutions were also tolerated as **3b** and **3c** were produced in excellent yields of 85% and 83%, respectively, though **3c** was formed in poorer diastereoselectivities (68:32) than **3b** (89:11). Moderate diastereoselectivity and yield were also observed with *o*-Br substitution, in which **3g** was isolated in 65% yield (dr 69:31). An electron-donating *p*-OMe group was tolerated, and **3h** was obtained in 68% yield and good diastereoselectivity (85:15). However, no formation of the desired product was observed with mesityl nitrone (**1p**). Lastly, when a phenyl ring was replaced with a cyclohexyl

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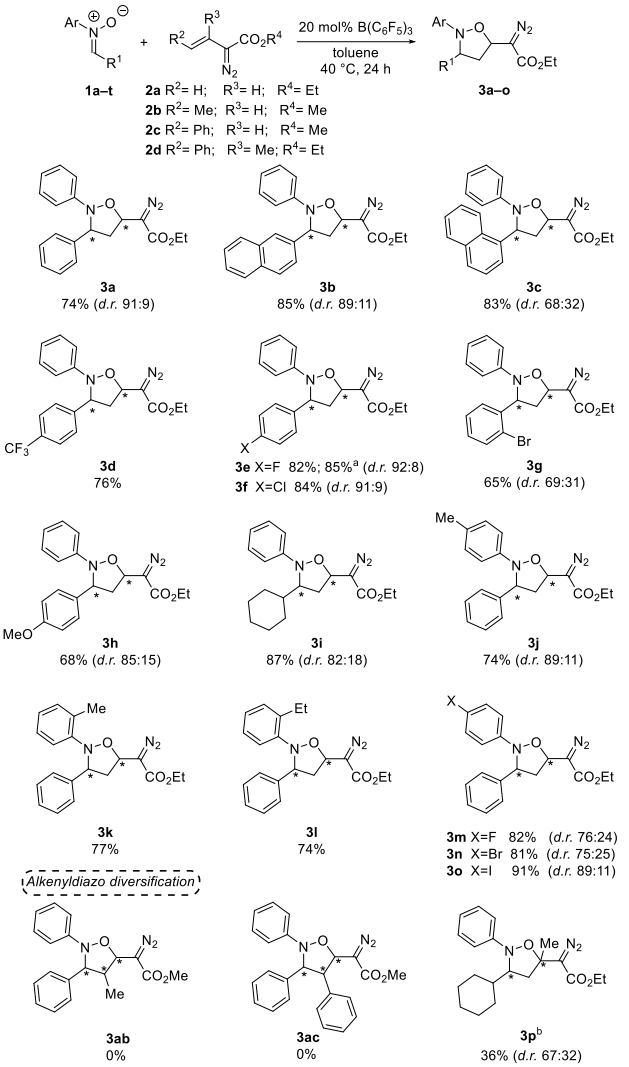
Scheme 3. Substrate Scope of the $B(C_6F_5)_3$-Catalyzed Cycloaddition Reaction of Vinyldiazo Esters with Nitrones



[a]Reaction carried out on a 1.0 mmol scale. [b]Reaction carried out at room temperature for 3 days.

moiety, the isoxazolidine-derivative **3i** was formed in excellent yield (87%) and in good diastereoselectivity (82:18). Subsequently, nitrones with different *N*-aryl substitutions (**1j**−**1o**, see Figure S1) were explored. In general, good to excellent yields (82−91%) and diastereoselectivities (up to 89:11) were obtained with halogen substitutions at the *para*-position (**3m**−**3o**). Moreover, the isoxazolidine products **3j** (*p*-Me), **3k** (*o*-Me), and **3l** (*o*-Et) with electron-donating alkyl groups were formed in 74−77% yields and in excellent diastereoselectivities. However, when a nitrone with a stronger electron-donating *p*-OMe group (**1q**) was employed, the reaction resulted in less than 5% of the desired product. Additionally, nitrones with two naphthyl substitutions (**1r**) or an *N*-alkyl group (**1s**) failed to react. Additionally, we screened internal alkenyldiazo esters bearing methyl (**2b**) and phenyl (**2c**) substitutions; however, these did not react with the nitrone **1a**. Alkenyldiazo ester **2d** afforded the desired isoxazolidine **3p** bearing a quaternary stereocenter, but a lower temperature and longer reaction time was required. Lastly, this methodology also proved applicable on a larger scale. Reaction of nitrone **1e** with the alkenyldiazo ester **2a** on a 1.0 mmol scale formed the isoxazolidine **3f** in 85% yield (92:8).

Crystals of product **3i** were grown by slow evaporation from CH_2Cl_2, whose structure was elucidated by single-crystal X-ray diffraction. The obtained crystal structure (Figure 1, left) revealed (*R*,*R*) stereochemistry, rendering *anti*-**3i** to be the major diastereoisomer. In the previously reported gold-catalyzed isoxazolidine formation by Liu et al., the *syn* diastereoisomer was obtained.[3b] We propose that the alternate selectivity observed in our study is likely due to the large steric demand of the borane catalyst as seen in other $B(C_6F_5)_3$-catalyzed cycloaddition reactions.[9]

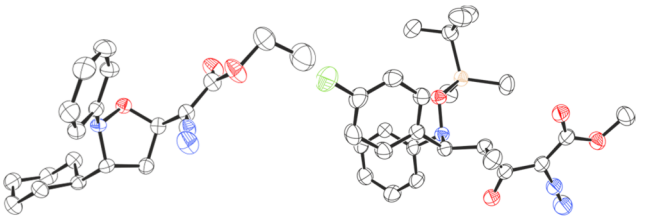
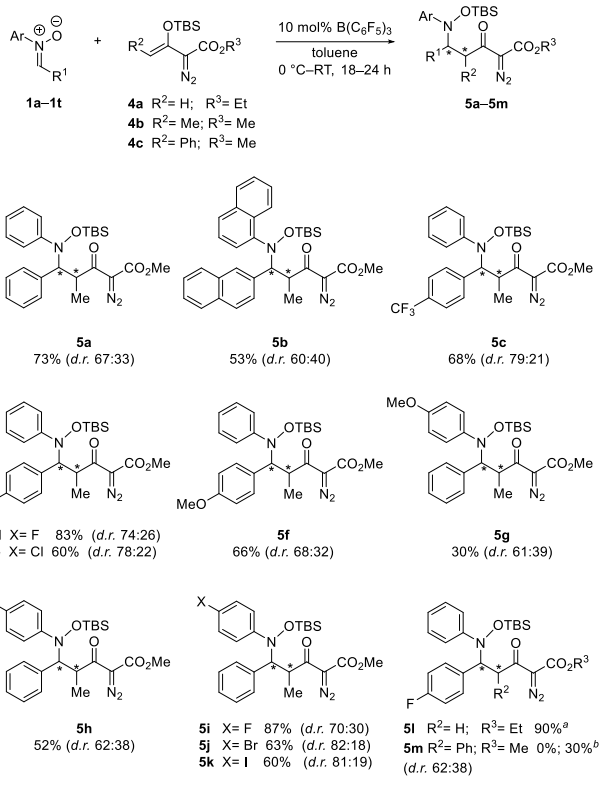


Figure 1. Solid-state structures of **3i** (left) and **5d** (right). Carbon: black; oxygen: red; nitrogen: blue; fluorine: green; silicon; beige. H atoms omitted for clarity. Thermal ellipsoids drawn at 50% probability.

Interestingly, when enol diazoacetate (**4a**) was reacted with nitrone **1e**, the expected [3 + 2] cycloaddition product was not observed and instead the Mukaiyama−Mannich product **5l** was obtained in 90% yield (Scheme 4). Similar results have

Scheme 4. Substrate Scope for the $B(C_6F_5)_3$-Catalyzed Mukaiyama−Mannich Addition Reactions



[a]20 mol % $B(C_6F_5)_3$, 40 °C. [b]Reaction carried out in 1,2-dichloroethane.

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previously been reported in the presence of Cu- and Mg-based Lewis acids.[3a,d,e] These observations led us to investigate the Mukaiyama−Mannich addition reaction. First, the optimized reaction conditions for the cycloaddition reaction (Table 1, entry 12) were tested for the Mukaiyama−Mannich addition with enol diazoacetate **4b** (R^2 = Me) and nitrone **1e**. Product **5d** was obtained in an excellent yield of 83% and in moderate diastereoselectivity (73:27). Lower temperatures (0 °C−room temperature) gave almost identical yields and diastereoselectivities (83% and 74:26 respectively). A lower catalytic loading of 10 mol % was also tested, and product **5d** was obtained in equivalent yield (83%).

The optimized reaction conditions for the Mukaiyama−Mannich reaction were set to 0 °C to room temperature with 10 mol % catalyst loading, and a scope was explored (Scheme 4). The product **5d** was isolated as a white crystalline solid, and its solid-state structure was elucidated by single-crystal X-ray diffraction (Figure 1, right) to reveal the *anti*-diastereoisomer (*anti*-**5d**) as the major product.

Investigation of the reaction scope revealed products bearing electron-withdrawing groups at the *para* position of R^1 = aryl (**5c**−**5e**) were formed in good to excellent yields (60−83%), with the best dr observed for *p*-CF_3 [79:21 (**5c**)] substitution. Mukaiyama−Mannich addition products with neutral (**5a**) and electron-donating *p*-OMe (**5f**) groups were obtained in yields of 73% and 66%, respectively, in moderate diastereoselectivities [67:33 (**5a**)] and [68:32 (**5f**)]. Similar observations were noticed with varying *N*-aryl substitution. Products with *p*-F (**5i**), *p*-Br (**5j**), and *p*-I (**5k**) substitutions were formed in up to 87% yield and with very good diastereoselectivities (up to 82:18).

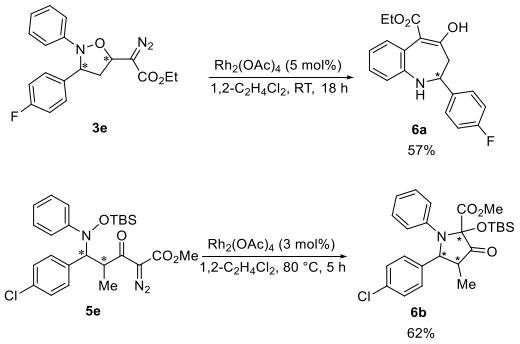
A more moderate yield of 52% and diastereoselectivity (62:38) was observed with a *p*-Me moiety (**5h**). Notably, the previously limiting substrates for the [3 + 2] cycloaddition reactions, *p*-OMe (**1q**) and dinaphthyl nitrone (**1r**), reacted with the enoldiazo ester **4b** giving **5g** (30%) and **5b** (53%). On the other hand, cyclohexyl (**1i**), mesityl (**1p**), and *N*-alkyl (**1s**) nitrones failed to react. Lastly, when the more sterically hindered enoldiazo ester (**4c**) was reacted with nitrone (**1e**), no product formation was observed. However, by changing the solvent to 1,2-dichloroethane, product (**5m**) was obtained, though in poor yield (30%).

Using our methodology both the isoxazolidine and Mukaiyama−Mannich addition products maintain the diazo functionality intact, which could be used for further functionalization. As a proof of concept, we took inspiration from the works of Doyle[3e] and Liu,[3b] and we subjected our substrates to the metal-catalyzed decomposition of the diazo functionality (Scheme 5).

$Rh_2(OAc)_4$ (5 mol %) proved to be a good catalyst for the synthesis of benzo[*b*]azepine cores from **3a** generating **6a** in 57% yield. Interestingly, by using $B(C_6F_5)_3$ (10 mol %) only 10% **6a** was formed. $Rh_2(OAc)_4$ (3 mol %) could also catalyze the formation of pyrrolidinone **6b** from the Mukayiama−Mannich product **5e**.

In summary, we have developed a transition-metal-free, Lewis acid catalyzed diastereoselective method toward highly functionalized isoxazolidine-derived diazo compounds in yields up to 91%. Interestingly, the diastereoselectivity observed in these reactions is opposite to that observed with similar gold-catalyzed transformations offering complementarity to transition-metal-catalyzed processes. Moreover, we have demonstrated and utilized the divergent reactivities of vinyldiazo compounds with nitrones through the substitution pattern present in the alkenyldiazo ester. To this end, we obtained Mukaiyama−Mannich addition diazo products in up to 90% yield. As such, a diverse pool of highly functionalized diazo compounds has been presented. Their further transformation toward medicinally relevant scaffolds has also been demonstrated.

Scheme 5. Further Functionalization of the Isoxazolidine and Mukaiyama−Mannich Addition Products



■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information. Information about the data that underpins the results presented in this article can be found in the Cardiff University data catalogue at 10.17035/d.2023.0236343549.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c04198.

Experimental procedures, full characterization of products, copies of ^1H, ^{13}C, ^{19}F NMR spectra, copies of mass spectra, and the X-ray crystallographic structures of compounds **3i** and **5e** (PDF)

Elemental composition data (ZIP)

Accession Codes

CCDC 2192556−2192557 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Cheng, Q.-Q.; Yu, Y.; Yedoyan, J.; Doyle, M. P. Vinyldiazo Reagents and Metal Catalysts: A versatile Toolkit for Heterocycle and Carbocycle Construction. *ChemCatChem.* **2018**, *10*, 488−496. (b) López, E.; González-Pelayo, S.; López, L. A. Recent Developments in Coinage Metal Catalyzed Transformations of Stabilized Vinyldiazo Compounds: Beyond Carbenic Pathways. *Chem. Rec.* **2017**, *17*, 312−315. (c) Cheng, Q.−Q.; Deng, Y.; Lankelma, M.; Doyle, M. P. Cycloaddition reactions of enoldiazo compounds. *Chem. Soc. Rev.* **2017**, *46*, 5425−5443. For selected examples, see: (d) Cheng, Q.−Q.; Lankelma, M.; Wherritt, D.; Arman, H.; Doyle, M. P. Divergent Rhodium-Catalyzed Cyclization Reactions of Enoldiazoacetamides with Nitrosoarenes. *J. Am. Chem. Soc.* **2017**, *139*, 9839−9842. (e) Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. Highly Selective Catalyst-Directed Pathways to Dihydropyrroles from Vinyldiazoacetates and Imines. *J. Am. Chem. Soc.* **2003**, *125*, 4692−4693.

(2) For selected examples, see: (a) Dong, K.; Xu, X.; Doyle, M. P. Copper (I)-Catalyzed Highly enantioselective [3 + 3]-Cycloaddition of γ-Alkyl Enoldiazoacetates with Nitrones. *Org. Chem. Front.* **2020**, *7*, 1653−1657. (b) López, E.; Lonzi, G.; González, J.; López, L. A. Gold-Catalyzed Intermolecular formal (3 + 2) Cycloaddition of Stabilized Vinyldiazo Derivatives and Electronically Unbiased Allenes. *Chem. Commun.* **2016**, *52*, 9398−9401. (c) Qin, Ch.; Davies, H. M. L. Rh_2(*R*-TPCP)$_4$-Catalyzed Enantioselective [3 + 2]-Cycloaddition between Nitrones and Vinyldiazoacetates. *J. Am. Chem. Soc.* **2013**, *135*, 14516−14519. (d) Xu, X.; Zavalij, P. J.; Doyle, M. P. A Donor−Acceptor Cyclopropene as a Dipole Source for a Silver (I) Catalyzed Asymmetric Catalytic [3+ 3]-Cycloaddition with Nitrones. *Chem. Commun.* **2013**, *49*, 10287−10289. (e) Wang, X.; Abrahams, Q. M.; Zavalij, P. Y.; Doyle, M. P. Highly Regio- and Stereoselective Dirhodium Vinylcarbene Induced Nitrone Cycloaddition with Subsequent Cascade Carbenoid Aromatic Cycloaddition/N−O Cleavage and Rearrangement. *Angew. Chem., Int. Ed.* **2012**, *51*, 5907−5910.

(3) (a) Meng, X.; Pan, H.; Zhu, G.; Zhang, X. Highly Efficient Mukaiyama-Mannich Addition of α-Diazo Silyl Enolate with Nitrones Catalyzed by MgI_2 Etherate. *Tetrahedron* **2020**, *76*, 131167−131174. (b) Pagar, V. V.; Liu, R.-S. Gold-Catalyzed Cycloaddition Reactions of Ethyl Diazoacetate, Nitrosoarenes, and Vinyldiazo Carbonyl Compounds: Synthesis of Isoxazolidine and Benzo[*b*]azepine Derivatives. *Angew. Chem., Int. Ed.* **2015**, *54*, 4923−4926. (c) Jadhav, A. P.; Pagar, V. V.; Liu, R.-S. Development of a Povarov Reaction/Carbene Generation Sequence for Alkenyldiazocarbonyl Compounds. *Angew. Chem., Int. Ed.* **2012**, *51*, 11809−11813. (d) Qian, Y.; Xu, X.; Wang, X.; Zavalij, P. J.; Hu, W.; Doyle, M. P. Rhodium(II)-and Copper(II)-Catalyzed Reactions of Enol Diazoacetates with Nitrones: Metal Carbene versus Lewis Acid Directed Pathways. *Angew. Chem., Int. Ed.* **2012**, *51*, 5900−5903. (e) Xu, X.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. Multifunctionalized 3-Hydroxypyrroles in a Three-Step, One-Pot Cascade Process from Methyl 3-TBSO-2-diazo-3-butenoate and Nitrones. *Org. Lett.* **2011**, *13*, 6122−6125. (f) Doyle, M. P.; Kundu, K.; Russell, A. E. Catalytic Addition Methods for the Synthesis of Functionalized Diazoacetoacetates and Application to the Construction of Highly Substituted Cyclobutanones. *Org. Lett.* **2005**, *7*, 5171−5174.

(4) For a review, see: (a) Dasgupta, A.; Richards, E.; Melen, R. L. Triarylborane Catalyzed Carbene Transfer Reactions Using Diazo Precursors. *ACS Catal.* **2022**, *12*, 442−452. For selected examples, see: (b) Babaahmadi, R.; Dasgupta, A.; Hyland, Ch. J. T.; Yates, B. F.; Melen, R. L.; Ariafard, A. Understanding the Influence of Donor−Acceptor Diazo Compounds on the Catalyst Efficiency of $B(C_6F_5)_3$ Towards Carbene Formation. *Chem.—Eur. J.* **2022**, *28*, No. e202104376. (c) Dasgupta, A.; Pahar, S.; Babaahmadi, R.; Gierlichs, L.; Yates, B. F.; Ariafard, A.; Melen, R. L. Borane Catalyzed Selective Diazo Cross-Coupling Towards Pyrazoles. *Adv. Synth. Catal.* **2022**, *364*, 773−780. (d) Wu, X.-Y.; Gao, W.-X.; Zhou, Y.-B.; Liu, M.-C.; Wu, H.-Y. Tris(pentafluorophenyl)borane-Catalyzed Oxygen Insertion Reaction of α-Diazoesters (α-Diazoamides) with Dimethyl Sulfoxide. *Adv. Synth. Catal.* **2022**, *364*, 750−754. (e) Stefkova, K.; Heard, M. J.; Dasgupta, A.; Melen, R. L. Borane Catalysed Cyclopropentaion of Arylacetylynes. *Chem. Commun.* **2021**, *57*, 6736−6739. (f) Dasgupta, A.; Babaahmadi, R.; Slater, B.; Ariafard, B. F.; Melen, R. L. Borane-Catalyzed Stereoselective C−H Insertion, Cyclopropanation, and Ring-Opening Reactions. *Chem.* **2020**, *6*, 2364−2381. (g) Dasgupta, A.; Stefkova, K.; Babaahmadi, R.; Gierlichs, L.; Ariafard, A.; Melen, R. L. Triarylborane-Catalyzed Alkenylation Reactions of Aryl Esters with Diazo Compounds. *Angew. Chem. Int. Ed.* **2020**, *59*, 15492−15496. (h) Mancinelli, J. P.; Wilkerson-Hill, S. M. Tris(pentafluorophenyl)borane-Catalyzed Cyclopropanation of Styrenes with Aryldiazoacetates. *ACS Catal.* **2020**, *10*, 11171−11176. (i) Santi, M.; Ould, D. M. C.; Wenz, J.; Soltani, Y.; Melen, R. L.; Wirth, T. Metal-Free Tandem Rearrangement/Lactonization: Access to 3,3-Disubstituted Benzofuran-2-(3*H*)-ones. *Angew. Chem., Int. Ed.* **2019**, *58*, 7861−7865. (j) San, H. H.; Wang, S.-J.; Jiang, M.; Tang, X.-Y. Boron-Catalyzed O−H Bond Insertion of α-Aryl α-Diazoesters in Water. *Org. Lett.* **2018**, *20*, 4672−4676. (k) Yu, Z.; Li, Y.; Shi, J.; Ma, B.; Liu, L.; Zhang, J. $(C_6F_5)_3B$ Catalyzed Chemoselective and *ortho*-Selective Substitution of Phenols with α-Aryl α-Diazoesters. *Angew. Chem., Int. Ed.* **2016**, *55*, 14807−14811.

(5) For a review, see: (a) Berthet, M.; Cheviet, T.; Dujardin, G.; Parrot, I.; Martinez, J. Isoxazolidine: A Privileged Scaffold for Organic and Medicinal Chemistry. *Chem. Rev.* **2016**, *116*, 15235−15283. For selected examples, see: (b) Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. Stereospecific Formal [3 + 2] Dipolar Cycloaddition of Cyclopropanes with Nitrosoarenes: An Approach to Isoxazolidines. *Angew. Chem. Ind. Ed.* **2014**, *53*, 5964−5968. (c) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. Total Synteses of Hyacinthacine A2 and 7-Deoxycasyarine by Cycloaddition to a Carbohydrate Derived Nitrone. *Tetrahedron Lett.* **2003**, *44*, 2315−2318.

(6) For a review, see: (a) Chiacchio, M. A.; Giofrè, S. V.; Romeo, R.; Romeo, G.; Chiacchio, U. Isoxazolidines as Biologically Active Compounds. *Curr. Org. Synth.* **2016**, *13*, 726−749. For selected examples, see: (b) Lynch, C. L.; Gentry, A. L.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J. CCR5 Antagonists: Bicyclic

Isoxazolidines as Conformationally Constrained N1-Substituted Pyrrolidines. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 677−679. (c) Tsuda, M.; Hirano, K.; Kubota, T.; Kobayashi, J. Pyrinodemin A Cytotoxic Pyridines Alkaloid with an Isozaxolidines Moiety from Sponge Amphimedon Sp. *Tetrahedron Lett.* **1999**, *40*, 4819−4820.

(7) (a) Nguyen, T. B.; Beauseigneur, A.; Martel, A.; Dhal, R.; Laurent, M.; Dujardin, G. Access to α-Substituted Amino Acid Derivatives via 1,3-Dipolar Cycloaddition of α-Amino Ester Derived Nitrones. *J. Org. Chem.* **2010**, *75*, 611−620. (b) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. N-Benzyl Asparate Nitrones: Unprecedented Single-Step Synthesis and [3 + 2] Cycloaddition Reactions with Alkenes. *Org. Lett.* **2008**, *10*, 4493−4496. (c) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. Homochiral α-$_D$- and β-$_D$-Isoxazolidinylthymidines via 1,3-Dipolar Cycloaddition. *J. Org. Chem.* **1999**, *64*, 9321−9327.

(8) Zheng, H.; Wang, K.; Faghihi, I.; Griffith, W. P.; Arman, H.; Doyle, M. P. Diverse Reactions of Vinyl Diazo Compounds with Quinone Oxonium Ions, Quinone Imine Ketals, and Eschenmoser's Salt. *ACS Catal.* **2021**, *11*, 9869−9874.

(9) Zhou, J.-H.; Jiang, B.; Meng, F.-F.; Xu, Y.-H.; Loh, T.-P. $B(C_6F_5)_3$: A New Class of Strong and Bulky Lewis Acid for *Exo*-Selective Intermolecular Diels−Alder Reactions of Unreactive Acyclic Dienes with α,β-Enals. *Org. Lett.* **2015**, *17*, 4432−4435.

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